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## The genetic code as a periodic table: algebraic aspects

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### Abstract

The systematics of indices of physico-chemical properties of codons and amino acids across the genetic code are examined. Using a simple numerical labelling scheme for nucleic acid bases,  $A = (-1, 0)$ ,  $C = (0, -1)$ ,  $G = (0, 1)$ ,  $U = (1, 0)$ , data can be fitted as low order polynomials of the 6 coordinates in the 64-dimensional codon weight space. The work confirms and extends the recent studies by Siemion et al. (1995) (BioSystems 36, 63-69) of the conformational parameters. Fundamental patterns in the data such as codon periodicities, and related harmonics and reflection symmetries, are here associated with the structure of the set of basis monomials chosen for fitting. Results are plotted using the Siemion one-step mutation ring scheme, and variants thereof. The connections between the present work, and recent studies of the genetic code structure using dynamical symmetry algebras, are pointed out.

**Keywords:** Physico-chemical properties, genetic code, periodicity, dynamical symmetry algebra.

# 1 Introduction and main results

Fundamental understanding of the origin and evolution of the genetic code (Osawa et al., 1991) must be grounded in detailed knowledge of the intimate relationship between the molecular biochemistry of protein synthesis, and the retrieval from the nucleic acids of the proteins' stored design information. However, as pointed out by Lacey and Mullins in 1983, although 'the nature of an evolutionary biochemical edifice must reflect ... its constituents, ... properties which were important to prebiotic origins may not be of relevance to contemporary systems'. Ever since the final elucidation of the genetic code, this conviction has led to many studies of the basic building blocks themselves, the amino acids and the nucleic acid bases. Such studies have sought to catalogue and understand the spectrum of physico-chemical characteristics of these molecules, and of their mutual correlations. The present work is a contribution to this programme.

Considerations of protein structure point to the fundamental importance of amino acid hydrophilicity and polarity in determining folding and enzymatic capability, and early work (Woese et al., 1966; Volkenstein, 1966; Grantham, 1974) concentrated on these aspects; Weber and Lacey (1978) extended the work to mono- and di-nucleosides. Jungck (1978) concluded from a compilation of more than a dozen properties that correlations between amino acids and their corresponding anticodon dinucleosides were strongest on the scale of hydrophobicity/hydrophilicity or of molecular volume/polarity. For a comprehensive review see Lacey and Mullins (1983).

Subsequent to this early work, using statistical sequence information, conformational indices of amino acids in protein structure have been added to the data sets (Goodman and Moore, 1977). Recently Siemion (1994a, 1994b) has considered the behaviour of these parameters across the genetic code, and has identified certain periodicities and pseudosymmetries present when the data is plotted in a certain rank ordering called 'one-step mutation rings', being generated by a hierarchy of cyclic alternation of triplet base letters (Siemion and Stefanowicz, 1992). The highest level in this hierarchy is the alternation of the second base letter, giving three major cycles based on the families *U*, *C* and *A*, each sharing parts of the *G* family. The importance of the second base in relation to amino acid hydrophilicity is in fact well known (Weber and Lacey, 1978; Lacey and Mullins, 1983; Taylor and Coates, 1989), and the existence of three independent correlates of amino acid properties, again associated with the *U*, *C* and *A* families, has also been statistically established by principal component analysis (Sjöström and Wöld, 1985).

Given the existence of identifiable patterns in the genetic code in this sense, it is of some interest and potential importance to attempt to describe them more quantitatively. Steps along these lines were taken in 1995 by Siemion et al. With a linear rank ordering of amino acids according to 'mutation angle'  $\pi k/32$ ,  $k = 1, \dots, 64$  along the one-step mutation rings, parameter  $P^\alpha$  was reasonably approximated by trigonometric functions which captured the essential fluctuations in the data.

The metaphor of a quantity such as the Siemion number  $k$ , allowing the genetic code to be arranged in a way which best reflects its structure, in analogy with elemental atomic number  $Z$  and the chemical periodic table, is an extremely powerful one. The present paper takes up this idea, but in a more flexible way which does not rely on a single parameter. Instead, a natural labelling scheme is used which is directly related to the combinatorial fact of the triplet base codon structure of the genetic code, and the four-letter base alphabet. Indeed, any bipartite labelling system which identifies each of the four bases *A*, *C*, *G*, *U*, extends naturally to a composite labelling for codons, and hence amino acids. We choose for bases two coordinates as  $A = (-1, 0)$ ,  $C = (0, -1)$ ,  $G = (0, 1)$ ,  $U = (1, 0)$ , so that codons are labelled as ordered sextuplets, for example  $ACG = (-1, 0, 0, -1, 0, 1)$ .

In quantitative terms, any numerical indices of amino acid or codon properties, of physico-

chemical or biological nature, can then be modelled as some functions of the coordinates of this codon ‘weight space’. Because of other algebraic approaches to the structure of the genetic code, we take polynomial functions (for simplicity, of as low order as possible). This restriction does not at all exclude the possibility of periodicities and associated symmetry patterns in the data. In fact, as each of the six coordinates takes discrete values  $0, \pm 1$ , appropriately chosen monomials can easily reproduce such effects (with coefficients to be fitted which reflect the relative strengths of various different ‘Fourier’ components). Quite simply, the directness of the linear rank ordering, as given by the Siemion number  $k$ , which suggests Fourier series analysis of the data, is here replaced by a more involved labelling system, but with numerical data modelled as simple polynomial functions.

The main results of our analysis are as follows. In §2 the labelling scheme for nucleic acid bases is introduced, leading to  $4^N$ -dimensional ‘weight spaces’ for length- $N$  RNA strands: in particular, 16-dimensional for  $N = 2$ , and 64-dimensional for the sextuplet codon labelling ( $N=3$ ). For  $N = 2$  the dinucleoside hydrophilicity, dinucleotide hydrophobicity, and free energy of formation of 2-base RNA duplexes are considered. Displayed as linear plots (or bar charts) on a ranking from 1 to 16, the data have obvious symmetry properties, and corresponding basis monomials are identified, resulting in good fits. Only four coordinates are involved for these 16- part data sets (see table 1). Moving in §3 on to codon properties as correlated to those of amino acids, Siemion number  $k$  which establishes amino acid ranking by mutation angle is briefly reviewed. It is shown that the trigonometric approximation of Siemion et al. (Siemion et al., 1995) to the Chou-Fasman conformational parameters  $P^\alpha$ ,  $P^\beta$  (Chou and Fasman, 1975; Fasman, 1989) is effectively a four-parameter function which allows for periodicities of  $32/5$ ,  $8$ ,  $32/3$  and  $64$  codons. Again, simple basis monomials having the required elements of the symmetry structure of  $P^\alpha$  are identified, leading to a reasonable (four-parameter) fit. Results are displayed as Siemion mutation-angle plots.  $P^\beta$  is treated in a similar fashion. The method established in §§2 and 3 is then applied in §4 to other amino acid properties, including relative hydrophilicity (Weber and Lacey, 1978) and Grantham polarity (Grantham, 1974). It is clearly shown that appropriate polynomial functions can be fitted to most of them (amino acid data is summarised in table 2).

In §5 some concluding remarks, and outlook for further development of these ideas are given. It is emphasised that, while the idiosyncracies of real biology make it inappropriate to regard this type of approach as anything but approximate, nonetheless there may be some merit in a more rigorous follow up to establish our conclusions in a statistically valid way. This is particularly interesting in view of the appendix, §A. This gives a brief review of algebraic work based on methods of dynamical symmetries in the analysis of the excitation spectra of complex systems (such as atoms, nuclei and molecules), which has recently been proposed to explain the origin and evolution of the genetic code. Specifically, it is shown how the labelling scheme adopted in the paper arises naturally in the context of models, based either on the Lie superalgebra  $A_{5,0} \sim sl(6/1)$ , or the Lie algebra  $B_6 \sim so(13)$ , or related semisimple algebras. The origins and nature of the polynomial functions adopted in the paper, and generalisations of these, are also discussed in the algebraic context. The relationship of the present paper to the dynamical symmetry approach is also sketched in §5 below.

## 2 Codon systematics

Ultimately our approach involves a symmetry between the 4 heterocyclic bases U,C,A,G commonly occurring in RNA. A logical starting point then, is to consider the physical properties of small RNA molecules. Dinucleosides and dinucleotides in particular are relevant in the informa-

tional context of the genetic code and anticode, and moreover are the building blocks for larger nucleic acids (NA's). What follows in this section is a numerical study of some properties of NA's consisting of 2 bases, while in later sections NA's with 3 bases (i.e. codons and anticodons) are considered in the context of the genetic code as being correlated with properties of amino acids.

As mentioned in the introduction, we give each NA base coordinates in a two-dimensional 'weight space', namely  $A = (-1, 0)$ ,  $C = (0, -1)$ ,  $G = (0, 1)$ ,  $U = (1, 0)$  with the axes labelled  $d, m$  respectively \*. Dinucleosides and dinucleotides are therefore associated with four coordinates  $(d_1, m_1, d_2, m_2)$ , *e.g.*  $AC = (-1, 0, 0, -1)$  with subscripts referring to the first and second base positions.

The physical properties of nucleic acids we choose to fit to are the relative hydrophilicities  $R_f$  of the 16 dinucleoside monophosphates as obtained by Weber and Lacey (1978), the relative hydrophobicity  $R_x$  of dinucleotides as calculated by Jungck (Jungck, 1978) from the mononucleotide data of Garel et al. (1973), and the 16 canonical (Crick-Watson) base-pair stacking parameters of Xia et al. (1998) used to compute the free heat of formation  $G_{37}^0$  of formation of duplex RNA strands at 37° Centigrade.

It should be noted that the dinucleoside quantity  $R_x$  was computed as the product of experimentally derived  $R_x$  values for mononucleotides under the assumption that this determines the true dinucleotide values to within 95 %. A result of this is that  $R_x$  is automatically the same for dinucleotides  $5' - XY - 3'$  and  $5' - YX - 3'$ , (naturally the same holds for molecules with the reverse orientation); thus  $R_x$  is at best an approximate symmetry.

The 16 Turner free-energy parameters are a subset of a larger number of empirically determined thermodynamic "rules of thumb" (see Xia et al., 1998; Mathews et al. 1999, for the most recent results), developed to predict free heats of formation of larger RNA and DNA molecules. The possibility that these rules have an underlying group-theoretical structure is a consideration for a future work. For now it suffices to observe that due to geometry (see table 1) the duplex formed by  $5' - XY - 3'$  with  $3' - \bar{Y}\bar{X} - 5'$  is just a rotated version of the duplex  $5' - \bar{X}\bar{Y} - 3'$  with  $3' - YX - 5'$ . Here  $\bar{X}$  denotes the Crick-Watson complementary base to  $X$ . Furthermore the duplexes formed by so-called "self-complementary" dinucleosides ( $5' - GC - 3'$  with  $5' - CG - 3'$  and  $5' - AU - 3'$  with  $5' - UA - 3'$ ) are thermodynamically suppressed due to the extra rotational symmetry (i.e there are 2 ways such a duplex can form) and one needs to include extra monomials to compensate for this. It is easy to see that the above rotational symmetry corresponds to the change of coordinates

$$(d_1, m_1, d_2, m_2) \rightarrow (-d_2, -m_2, -d_1, -m_1) \quad (1)$$

and thus we need look only at monomials which respect this symmetry, for example  $m_1 - m_2$ ,  $d_1 d_2$  and  $(d_1 m_2 + d_2 m_1)$ . The least-squares fit to the most recent values of the Turner parameters (Xia et al., 1998) is shown in figure 1 and is given by

$$\begin{aligned} -G_{37}^0(d_1, m_1, d_2, m_2) = & 1.133 + 0.02((m_1 + d_1)m_2 + d_2(m_1 - d_1)) + 1.001(m_1^2 + m_2^2) \\ & - 0.1d_1 d_2 + 0.035(d_1 - d_2) + 0.1(m_1 - m_2) \\ & + 0.165m_1 m_2(m_2 - m_1 + 1) + 0.0225d_1 d_2(d_2 - d_1 - 1). \end{aligned} \quad (2)$$

Here we have considered all linear and quadratic terms respecting the symmetry Eq.(1) and added cubic symmetry-breaking terms which are specific to the self-complementary duplexes.

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\*The choice  $(\pm 1, \pm 1)$  and  $(\pm 1, \mp 1)$  for the four bases simply represents a 45° rotation of the adopted scheme, which turns out to be more convenient for our purposes. The nonzero labels at each of the four base positions are given by the mnemonic 'diamond'.

The number of monomials may be reduced with the identities:

$$d_i^2 = 1 - m_i^2 \quad (3)$$

$$m_i d_i = 0, \quad (4)$$

Encouraged by this success we attempt a similar fit to  $R_f$  and  $R_x$ . While there is no obvious underlying symmetry *a priori* as in the previous discussion, one might expect these properties to be anti-correlated and so the same set of monomials is considered for each. Qualitatively faithful fits may be obtained using a small number of monomials, as shown in figure 2. The functions

$$R_f(d_1, m_1, d_2, m_2) = 0.191 - 0.087(d_1^2 + d_2^2) + 0.09d_1 + 0.107d_2 - 0.053m_1 - 0.077m_2, \quad (5)$$

$$R_x(d_1, m_1, d_2, m_2) = 0.3278 + 0.093(d_1^2 + d_2^2) - 0.1814(d_1 + d_2) + 0.0539(m_1 + m_2) \quad (6)$$

are seen to compare favourably to the experimental values and that moreover  $R_f$  and  $R_x$  are roughly anti-correlated. Thus fitting to these using the same set of monomials seems to be a valid procedure in this initial approximation.

### 3 Amino acid conformational parameters

As a case study for amino acid properties (as opposed to their correlated codon properties in §2 above) we consider the structural conformational parameters  $P^\alpha$  and  $P^\beta$ , which have been discussed by Siemion (1994a, 1994b). In 1995 Siemion et al. introduced a quantity  $k$ ,  $k = 1, \dots, 64$ , which defined the so-called ‘mutation angle’  $\pi k/32$  for a particular assignment of codons (and hence of amino acids) in rank ordering. This is a ramification of the four-ring ordering used above for plots (expanded from 16 to 64 points), and arises from a certain hierarchy of one-step base mutations. It assigns the following  $k$  values to the  $NN'Y$  and  $NN'R$  codons<sup>†</sup>

1	3	5	7	9	11	13	15
<i>GGY</i>	<i>GGR</i>	<i>GAR</i>	<i>GAY</i>	<i>AAY</i>	<i>AAR</i>	<i>CAR</i>	<i>CAY</i>
17	19	21	23	25	27	29	31
<i>UAY</i>	<i>UAR</i>	<i>UGR</i>	<i>UGY</i>	<i>UCY</i>	<i>UCR</i>	<i>GCR</i>	<i>GCY</i>
33	35	37	39	41	43	45	47
<i>ACY</i>	<i>ACR</i>	<i>CCR</i>	<i>CCY</i>	<i>CGY</i>	<i>CGR</i>	<i>CUR</i>	<i>CUY</i>
49	51	53	55	57	59	61	63
<i>UUY</i>	<i>UUR</i>	<i>GUR</i>	<i>GUY</i>	<i>AUY</i>	<i>AUR</i>	<i>AGR</i>	<i>AGY</i>

wherein (as in the ‘four ring’ scheme) the third base alternates as  $\dots - G, A - U, C - C, U - A, G - \dots$  for purine-pyrimidine occurrences  $\dots - R - Y - Y - R - \dots$ . This ‘mutation ring’ ordering corresponds to a particular trajectory around the diamond-shaped representation of the genetic code (figure 3), which is pictured in figure 4 (Siemion, 1994a) where nodes have been labelled by amino acids.

Inspecting the trends of assigned  $P^\alpha$  values for the amino acids ordered in this way, a suggestive 8-codon periodicity, and a plausible additional  $C_2$  rotation axis about a spot in the centre of the diagram, have been identified (Siemion, 1994a, 1994b). Figure 5 gives various fits to this data, as follows. Firstly, consideration of the modulation of the peaks and troughs of the

<sup>†</sup> Individual codons are labelled so that these  $Y, R$  positions are at the midpoints of their respective  $k$  intervals. Thus *GGR* occupies  $0 \leq k \leq 2$ , with nominal  $k = 1$  and codons  $k(\text{GGA}) = 0.5$ ,  $k(\text{GGC}) = 1.5$ .

period-8 component, on either side of the centre at  $k = 0$ , leads to a trigonometric function (Siemion et al., 1995).

$$P_S^\alpha(k) = 1.0 - [0.32 + 0.12 \cos(\frac{k\pi}{16})] \cos(\frac{k\pi}{4}) - 0.09 \sin(\frac{k\pi}{32}) \quad (7)$$

where the parameters are estimated simply from the degree of variation in their heights (and  $0.44 = 0.32 + 0.12$  is the average amplitude). Least-squares fitting of the same data in fact leads to a similar function,

$$P_L^\alpha(k) = 1.02 - [0.22 + 0.21 \cos(\frac{k\pi}{16})] \cos(\frac{k\pi}{4}) + 0.005 \sin(\frac{k\pi}{32}). \quad (8)$$

From the point of view of Fourier series, however, the amplitude modulation of the codon period-8 term in  $P_S^\alpha$  or  $P_L^\alpha$  merely serves to add extra beats of period  $32/5$  and  $32/3$  of equal weight 0.06; an alternative might then be to allow different coefficients. This gives instead the fitted function

$$P_F^\alpha(k) = 1.02 - 0.22 \cos(\frac{k\pi}{4}) - 0.11 \cos(\frac{3k\pi}{16}) - 0.076 \cos(\frac{5k\pi}{16}) \quad (9)$$

which has no  $\sin(\frac{k\pi}{32})$  term, but is almost indistinguishable from equation (8) above (note that  $0.22 + 0.21 \simeq 0.22 + 0.11 + 0.07 \simeq 0.32 + 0.12 = .44$ ). In figure 5 the  $P^\alpha$  data is displayed as a histogram along with  $P_S^\alpha$ , and  $P_F^\alpha$  above; as can be seen, both fits show similar trends, and both have difficulty in reproducing the data around the first position codons of the  $C$  family in the centre of the diagram (see caption to figure 5).

Basing the systematics of the genetic code on numerical base labels, as advocated in the present work, a similar analysis to the above trigonometric functions is straightforward, but now in terms of polynomials over the six codon (*i.e.* trinucleotide) coordinates  $(d_1, m_1, d_2, m_2, d_3, m_3)$ . There is no difficulty in establishing basic 8-codon periodic functions; combinations such as  $\frac{3}{2}d_3 - \frac{1}{2}m_3$  (with values  $-\frac{3}{2}, -\frac{1}{2}, \frac{1}{2}, +\frac{3}{2}$  on  $A, G, C, U$ ), or more simply the perfect  $Y/R$  discriminator  $d_3 - m_3$  (with values  $-1, +1$  on  $R, Y$  respectively) can be assumed. Similarly, terms such as  $d_1 \pm m_1$  have period 16, and  $d_2 \pm m_2$  have period 64. The required modulation of the 8-codon periods can also be regained by including in the basis functions for fitting a term such as  $d_2^2$ , and finally an enhancement of the  $C$  ring family boxes  $GCN, CCN$  is provided by the cubic term  $m_1m_2(m_2 - 1)$ . The resulting least-squares fitted function is

$$P_6^\alpha(d_1, m_1, d_2, m_2, d_3, m_3) = 0.86 + 0.24d_2^2 + 0.21m_1m_2(m_2 - 1) - 0.02(d_3 - m_3) - 0.075d_2^2(d_3 - m_3) \quad (10)$$

and is plotted against the  $P^\alpha$  data in figure 7. The resulting fit<sup>‡</sup> is rather insensitive to the weights of  $d_3$  and  $m_3$  (allowing unconstrained coefficients in fact results in identical weights  $\pm 0.02$  for the linear terms and  $-0.064, +0.085$  for the  $d_2^2$  coefficients respectively). It should be noted that, despite much greater fidelity in the  $C$  ring,  $P_6^\alpha$  shows similar features to the least squares trigonometric fits  $P_L^\alpha$  and  $P_F^\alpha$  in reproducing the 8-codon periodicity less clearly than  $P_S^\alpha$  (see figure 5). This indicates either that the minimisation is fairly shallow at the fitted functions (as suggested by the fact that  $P_L^\alpha$  and  $P_F^\alpha$  differ by less than  $\pm 0.01$  over one period), or that a different minimisation algorithm might yield somewhat different solutions. To show the possible range of acceptable fits, a second monomial is displayed in figure 7 whose  $d_2^2(d_3 - m_3)$  coefficient

<sup>‡</sup> In contrast to the trigonometric fits which are only intended to fit the data for specified codons (indicated by the dots in figure 5), the least-squares fit is applied for the polynomial functions to all 64 data points. See Siemion (Siemion et al., 1995) and the captions to figures 5 and 7

is chosen as  $-0.2$  rather than  $-0.075$ . This function plays the role of the original estimate  $P_S^\alpha$  of figure 5 in displaying a much more pronounced eight-codon periodicity than allowed by the least-squares algorithm.

The nature of the eight-codon periodicity is related to the modulation of the conformational status of the amino acids through the  $R$  or  $Y$  nature of their third codon base (Siemion and Siemion, 1994). A sharper discriminator of this is the difference  $P^\alpha - P^\beta$ , which suggests that a more appropriate basis for identifying numerical trends is with  $P^\alpha - P^\beta$  (the helix-forming potential) and  $P^\alpha + P^\beta$  (generic-structure-forming potential). Although we have not analysed the data in this way, this is indirectly borne out by separate fitting (along the same lines as above) of  $P^\beta$ , for which *no* significant component of  $(d_3 - m_3)$  is found. A typical five-parameter fit, independent of third base coordinate, is given by

$$P_6^\beta(d_1, m_1, d_2, m_2, d_3, m_3) = 1.02 + .26d_2 + .09d_1^2 - .19d_2(d_1 - m_1) - .1d_1m_2(m_2 - 1) - .16m_1^2m_2(m_2 - 1). \quad (11)$$

Figure 8 shows that this function does indeed average over the third base  $Y/R$  fluctuations evident in the  $A$  family data. A major component appears to be the dependence on  $(d_1 - m_1)$ , that is, on the  $Y/R$  nature of the *first* codon base, responsible for the major peaks and troughs visible on the  $A$  and  $U$  rings (and reflected in the  $d_2(d_1 - m_1)$  term). The cubic and quartic terms follow the modulation of the data on the  $C$  ring.

The suggested pseudosymmetries of the conformational parameters are important for trigonometric functions of the mutation angle, and for polynomial fits serve to identify leading monomial terms with simple properties. The  $d_2(d_1 - m_1)$  term in the fit of  $P_6^\beta$  above has been noted already in this connection. In the case of  $P^\alpha$ , it should be noted that an offset of 2 codons in the position of a possible  $C_2$  rotation axis (from  $k = 34$ , between  $ACY$  and  $ACR$  to  $k = 32$ , after  $GCY$ ) changes the axis from a pseudosymmetry axis (minima coincide with maxima after rotation) to a true symmetry axis (as the alignment of minima and maxima is shifted by four codons), necessitating fitting by a period-eight component which is *even* about  $k = 32$ . At the same time the large amplitude changes in the  $C$  ring appear to require an *odd* function, and are insensitive to whether the  $C_2$  axis is chosen at  $k = 32$  or  $k = 34$ . The terms in  $P_6^\alpha$  above have just these properties.

## 4 Other amino acid properties

In this section we move from the biologically-measured conformational parameters to biochemical indices of amino acid properties. Two of the most significant of these are the Grantham polarity (Grantham, 1974) and the relative hydrophilicity as obtained by Weber and Lacey (1978). Variations in chemical reactivity have been considered (Siemion and Stefanowicz, 1992), but are not modelled here.

The composite Grantham index incorporates weightings for molecular volume and molecular weight, amongst other ingredients (Grantham, 1974). From figure 10 it is evident that a major pattern is a broad 16-codon periodicity (indicative of a term linear in  $d_2$ ). Additional smaller fluctuations coincide approximately with the 8-codon periodicity of the  $Y/R$  nature of the third base ( $d_3 - m_3$  dependence). Although there is much complex variation due to the first base, in the interests of simplicity, the following fitted function ignores this latter structure, and provides an approximate (2-parameter) model (see figure 10):

$$G_6(d_1, m_1, d_2, m_2, d_3, m_3) = 8.298 - 2.716d_2 - 0.14(d_3 - m_3). \quad (12)$$

The pattern of amino acid hydrophilicity is also seen to possess an 8-codon periodicity. The 4-parameter fitted function considered, which is plotted in fig. 9, is:

$$R_{f6}(d_1, m_1, d_2, m_2, d_3, m_3) = 0.816 - 0.038d_2 - 0.043m_2 + 0.022(d_3 - m_3) + 0.034(1 - d_2)d_2(d_3 - m_3) \quad (13)$$

As with the case of Grantham polarity, the 8-period extrema might be more 'in phase' with the data if codons were weighted according to usage, after the approach of Siemion (Siemion et al., 1995).

## 5 Conclusions and outlook

In this paper we have studied codon and amino acid correlations across the genetic code starting from the simplest algebraic labelling scheme for nucleic acid bases (and hence RNA or DNA strands more generally). The relationship between the rank ordering of amino acids according to Siemion number  $k$ ,  $k = 1, \dots, 64$ , and a description of codons based on 3 dichotomic labels, had been established (figures 3,4). In §2 several dinucleoside properties have been fitted as quadratic polynomials of the labels, and §3 and §4 have considered amino acid parameters as correlated to codons (trinucleotides), namely conformational parameters, Grantham polarity and hydrophilicity. The types of data considered for fitting in our approach include strictly physical information (amino acid molecular weight and volume), physico-chemical indices (for example, the semi-empirical indicators of dinucleoside free energy of formation, and the composite amino acid Grantham polarity), as well as biological measures (such as the conformational parameters, which are logarithmic measures of amino acid usage in structural protein elements). As pointed out in the introductory discussion, *all* of these measures should be considered as important aspects in the 'optimisation' of the genetic code (see also the remarks in the appendix, §A) In all cases acceptable algebraic fitting is possible, and various patterns and periodicities in the data are readily traced to the contribution of specific monomials in the least-squares fit.

As pointed out in the appendix, §A, our algebraic approach is a special case of more general dynamical symmetry schemes in which measurable attributes  $H$  are given as combinations of Casimir invariants of certain chains of embedded Lie algebras and superalgebras (Bashford et al. 1997, 1998; Hornos and Hornos, 1993; Schlesinger et. al 1998; Schlesinger and Kent, 1999; Forger et al., 1997). The identification by Jungck (1978) of two or three major characters, to which all other properties are strongly correlated, would similarly in the algebraic description mean the existence of two or three distinct, 'master' Hamiltonians  $H_1$ ,  $H_2$ ,  $H_3$ , ... (possibly with differing branching chains). In themselves these could be abstract and need not have a physical interpretation, but all other properties should be highly correlated to them,

$$K = \alpha_1 H_1 + \alpha_2 H_2 + \alpha_3 H_3. \quad (14)$$

Much has been made of the famous redundancy of the code in providing a key to a group-theoretical description (Hornos and Hornos, 1993; Forger et al. 1997). In the present framework (see also Bashford et al., 1997; 1998), codon degeneracies take second place to major features such as periodicity and other systematic trends across the genetic code. Thus for example the noted 8-codon periodicity of the conformational parameter  $P^\alpha$  allows the  $Y$  codons for  $k = 25$ ,  $UCY$ , and  $k = 63$ ,  $AGY$  both to be consistent with *ser* (as the property attains any given value twice per 8-codon period, at  $Y/R$  box  $k = 24 + 1 = 25$ , and again 4 periods later at the alternative phase  $k = 56 + 7 = 63$ ).



A related theme is the reconstruction of plausible ancestral codes based on biochemical and genetic indications of the evolutionary youth of certain parts of the existing code. For example the anomalous features of arginine, *arg* which suggests that it is an ‘intruder’ has led (Jukes, 1973) to the proposal of a more ancient code using ornithine *orn* instead. This has been supported by the trigonometric fit to  $P^\alpha$  (Siemion et al., 1995; Siemion and Stefanowicz, 1996), as the inferred parameters for *orn* actually match the fitted function better than *arg* at the  $k = 43$ ,  $k = 61$  *CGR*, *AGR* codons. Such variations could obviously have some influence on the polynomial fitting, but at the present stage have not been implemented<sup>§</sup>.

To the extent that the present analysis has been successful in suggesting the viability of an algebraic approach, further work with the intention of establishing (14) in a statistically reliable fashion may be warranted. What is certainly lacking to date is any microscopic justification for the application of the techniques of dynamical symmetry algebras (but see Bashford et al., 1997,1998). However, it can be considered that in the path to the genetic code, the primitive evolving and self-organising system of information storage and directed molecular synthesis has been subjected to ‘optimisation’ (whether through error minimisation, energy expenditure, parsimony with raw materials, or several such factors). If furthermore the ‘space’ of possible codes has the correct topology (compact and convex in some appropriate sense), then it is not implausible that extremal solutions, and possibly the present code, are associated with special symmetries. It is to support the identification of such algebraic structures that the present analysis is directed.

After this work was completed, we received a paper (Frappat et al.,2000) which gives a similar analysis of dinucleotide properties and correlations between physical-chemical properties of amino acids and codons based on a particular algebraic scheme (see also Frappat et al., 1998). It should be emphasized that comparisons of such analyses based merely on the number of fitted parameters is not particularly illustrative at this preliminary stage. One could modify, for example, Eq.(2) by cubic or quadratic transformations with the intent to minimise the number of parameters, but our motivation is to employ physical symmetry properties in an intuitive way. The number of parameters reflects the fact that our analysis has no prior commitment to any given abstract algebraic scheme. Indeed reproducing the fitted  $G_{37}^0$  of (Frappat et al., 2000) requires a judicious choice of cubic monomial terms.

## Acknowledgements

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<sup>§</sup> The polynomial fits are to *all* 64 codons, not just those with greatest usage. In fact there is no particular difficulty with *arg* in the  $P_6^\alpha$  function (see figure 7).

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## A Appendix: Dynamical symmetry algebras and genetic code structure

The radical proposal of Hornos and Hornos (1993) to elucidate the genetic code structure using the methods of dynamical symmetry algebras drew attention to the relationship of certain symmetry-breaking chains in the Lie algebra  $C_3 \sim Sp(6)$  to the fundamental degeneracy patterns of the 64 codons. This theme has been taken up subsequently using various different Lie algebras (Schlesinger et al. 1998; Schlesinger and Kent, 1999; Forger et al., 1997) and also Lie superalgebras (Bashford et al., 1997, 1998, Forger and Sachse, 1998; Sorba and Sciarrino, 1998). In addition to possible insights into the code redundancy, a representation-theoretical description also leads to a code elaboration picture whereby evolutionary primitive, degenerate assignments of many codons to a few amino acids and larger symmetry algebras gave place, after symmetry breaking to subalgebras, to the incorporation of more amino acids, each with fewer redundant codons.

In (Bashford et al., 1997, 1998, Jarvis and Bashford, 1998) emphasis was given not to the patterns of codon redundancy as such, but rather to biochemical factors which have been recognised as fundamental keys to be incorporated in any account of evolution from a primitive coding system to the present universal one. Among these factors is the primacy of the second base letter over the first and third in correlating with such basic amino acid properties as hydrophilicity (Woese et al., 1966 ;Volkenstein, 1966). Also, the partial purine/pyrimidine dependence of the amino acid assignments within a family box further underlines the informational content of the third codon base (Siemion and Siemion, 1994) and necessitates a symmetry description which distinguishes the third base letter. In (Bashford et al., 1998) the amino acid degeneracy was replaced by the weaker condition of anticodon degeneracy, leading to a Lie superalgebra classification scheme using chains of subalgebras of  $A_{5,0} \sim sl(6/1)$  (see below for details).

A concomitant of any representation-theoretical description of the genetic code is the ‘weight diagram’ mapping the 64 codons to points of the weight lattice (whose dimension is the rank of the algebra chosen). Reciprocally, the line of reasoning advocated above and applied in (Bashford et al., 1998) to the case of Lie superalgebras suggests that *any description using dynamical symmetry algebras must be compatible with the combinatorial fact of the four-letter alphabet, three-letter word structure of the code*. The viewpoint adopted in the present paper is to explore the implications of generic labelling schemes of this type, independently of the particular choice of algebra or superalgebra. In particular, as pointed out in §2 above, the weight diagram is supposed to arise from labelling each of the three base letters of the codon alphabet with a pair of dichotomic variables. Thus the only technical structural requirement for Lie algebras and superalgebras compatible with the present work is the existence of a 6-dimensional maximal abelian (Cartan) subalgebra, and of 64-dimensional irreducible representations whose weight diagram has the geometry of a six-dimensional hypercube in the weight lattice. (The relationship between the base alphabet and the  $Z_2 \times Z_2$  Klein four-group has been discussed by Bertman and Jungck (1979). As examples of a Lie algebra and a Lie superalgebra with this structure, we here take the case of  $B_6 \sim SO(13)$  and  $A_{5,0} \sim sl(6/1)$  respectively (other examples would be  $SO(4)^3$ ,  $sl(2/1)^3$ ).

The orthogonal algebra  $SO(14)$  has been suggested (Schlesinger et al., 1998) as a unifying scheme for variants of the  $Sp(6)$  models (Hornos and Hornos, 1993; Forger et al., 1997). However, from the present perspective, it is sufficient to take spinor representations of the rank-6 odd orthogonal algebra  $SO(13)$  which have dimension 64. Consider the subalgebra chain

$$SO_{13} \supset SO_4^{(2)} \times SO_9$$

$$\begin{aligned}
& \supset SO_4^{(2)} \times SO_4^{(1)} \times SO_5^{(3)}; \\
SO_5^{(3)} & \supset SO_3^{(3)} \times SO_2^{(3)}, \quad \text{or} \\
SO_5^{(3)} \sim Sp_4^{(3)} & \supset Sp_2^{(3)} \times Sp_2^{(3)'},
\end{aligned}$$

where superscripts indicate base letter. The 64-dimensional representation splits into 4 16-plets at the first breaking stage (the four families labelled by second codon base letter, the latter being distinguished as a spinor  $(\frac{1}{2}, 0) + (0, \frac{1}{2})$  of  $SO_4^{(2)}$ ). The same pattern repeats for the first codon base  $SO_4^{(1)}$  providing a complete labelling of the 16 family boxes (fixed first and second base letter). The last stage gives two possible alternatives for the third base symmetry breaking: in the first, each family box would split into two doublets  $(\frac{1}{2}, \frac{1}{2}) + (\frac{1}{2}, -\frac{1}{2})$  of  $SO_3^{(3)} \times SO_2^{(3)}$ , corresponding to a perfect 32-amino-acid-code  $4 \rightarrow 2 + 2$ , or to  $Y/R$  degeneracy in anticodon usage; in the second case, breaking of  $Sp_2^{(3)'}$  to  $U_1^{(3)}$  yields a family box assignment  $2 \times (\frac{1}{2}, 0) + (0, +\frac{1}{2}) + (0, -\frac{1}{2})$  coinciding with a 48-amino-acid-code,  $4 \rightarrow 2 + 1 + 1$ , or to perfect  $Y$ -degeneracy and  $R$ -splitting in amino acid *usage*. In the eukaryotic code, the  $4 \rightarrow 2 + 1 + 1$  family-box-pattern of anticodon usage is seen, whereas in the vertebrate mitochondrial code, only partial  $4 \rightarrow 2 + 2$  family box splitting of anticodon usage is found (see below). Finally, the above labels are all (up to normalisation) of the form  $(0, \pm 1)$  or  $(\pm 1, 0)$  for each base letter (or  $(\pm 1, \pm 1)$  for the third base for one branching) showing that this group-theoretical scheme does indeed give a hypercubic geometry for the codon weight diagram.

The  $sl(6/1)$  superalgebra was advocated in a survey of possible Lie superalgebras relevant to the genetic code (Bashford et al. 1997,1998), and possesses irreducible, typical representations of dimension 64 which share many of the properties of spinor representations of orthogonal Lie algebras (in the family  $sl_{n/1}$  of Lie superalgebras this class of representations has dimension  $2^n$ ) and so can be compared with spinors of the even- and odd-dimensional Lie algebras of rank  $n$ , namely  $SO_{2n}$  and  $SO_{2n+1}$  respectively). The superalgebra branching chain related to the  $SO(13)$  chain described above is

$$\begin{aligned}
sl_{6/1} & \supset sl_2^{(2)} \times sl_{4/1} \\
& \supset sl_2^{(2)} \times sl_2^{(1)} \times sl_{2/1}^{(3)}; \\
sl_{2/1}^{(3)} & \supset sl_{1/1} \quad \text{or} \\
sl_{2/1}^{(3)} & \supset sl_2 \times U_1
\end{aligned}$$

where the last two steps correspond as above either to family box breaking to  $Y/R$  doublets (as in many of the anticodon assignments of the vertebrate mitochondrial code) or to a  $4 \rightarrow 2 + 1 + 1$  pattern (as in the anticodons of the eukaryotic code). The nature of the weight diagram follows from knowledge of the branching in each of the above embeddings. In fact both in the decomposition of the irreducible 64 to families of 16, and in that of the 16 to family boxes of 4, there are a doublet and two singlets of the accompanying  $sl_2^2$  and  $sl_1^2$  algebras, so that the diagonal Cartan element (magnetic quantum number) has the spectrum  $0, \pm \frac{1}{2}$ . A second diagonal label arises because there is also an additional commuting  $U_1$  generator at each stage with value  $\pm 1$  on the two singlets and 0 on the doublet. Alternatively, the additional label may be taken as the  $\pm 1$  or 0 shift in the noninteger Dynkin label of the commuting  $sl_{n/1}$  algebra ( $n = 4$  and  $n = 2$  respectively). Similar considerations apply to the last branching stage (Bashford et al., 1998), so that again the weight diagram has the hypercubic geometry assumed in the text of the paper.

In the dynamical symmetry algebra approach to problems of complex spectra, important physical quantities such as the energy levels of the system, and the transition probabilities for decays, are modelled as matrix elements of certain operators belonging to the Lie algebra or superalgebra. In particular, the Hamiltonian operator which determines the energy is assumed to be a linear combination of a set of invariants of a chain of subalgebras  $G \supset G_1 \supset G_2 \supset \cdots T$ :

$$H = c_1\Gamma_1 + c_2\Gamma_2 + \cdots + c_T\Gamma_T$$

for coefficients  $c_i$  to be determined. For states in a certain representation of the algebra  $G$ , the energy can often be evaluated once the hierarchy of representations of  $\supset G_1 \supset G_2 \supset \cdots T$  to which they belong is identified, as the invariants are functions of the corresponding representation labels.

As has been emphasised above, the discussion of fitting of codon and amino acid properties in the main body of the paper is independent of specific choices of Lie algebras or superalgebras. In fact, the polynomial functions of the 6 codon coordinates may simply be regarded as *generalised* invariants of the smallest subalgebra common to all cases, namely the 6-dimensional Cartan (maximal abelian) subalgebra  $T$  (so that there are several nonzero coefficients  $c_T$ , with all other  $c_i$  zero). This approach is thus complementary to detailed applications of a chosen symmetry algebra, where the coefficients  $c_i$  (including  $c_T$ ) might accompany a specific set of  $\Gamma_i$  (functions of the whole hierarchy of labels, whose form is fixed, depending on the subalgebra). However, because the weight labels used in the present work already provide an unambiguous identification of the 64 states, such functions of any possible additional labels are in principle determined as cases of the general expansions we have been studying. For this reason the present work, although deliberately of a generic nature, does indeed confirm the viability of the dynamical symmetry approach.

## Captions of Tables and figures

**Table 1:** Table of dinucleoside properties and predicted values from fits.  $G_{37}^0$ : Turner free-energy parameters at 37° in kcal mol<sup>-1</sup> (Xia et al., 1998) ;  $R_f$ : dinucleoside monophosphate relative hydrophilicity (Weber and Lacey, 1978);  $R_x$ : dinucleotide relative hydrophobicity (Jungck, 1978).

**Table 2:** Table of amino acid properties ( $P_{\alpha,\beta}$ : conformational parameters (Fasman, 1989);  $P_{Gr}$ : Grantham polarity (Grantham, 1974);  $R_f$ : Relative hydrophilicity (Weber and Lacey, 1978).

**Figure 1:** Least-squares fit (curve) to the Turner free-energy parameters (points) at 37° given by Eq. (2). Units are in kcal mol<sup>-1</sup>.

**Figure 2:** Least-squares fits for dinucleoside  $R_f$  (upper) and dinucleotide  $R_x$  (lower). Points are experimental values while the curves are least-squares fits given by Eqs.(5) and (6) respectively.

**Figure 3:** ‘Weight diagram’ for the genetic code, arising as the superposition of two projections of the 6-dimensional space of codon coordinates onto planes corresponding to coordinates for bases of the first and second codon letters, and an additional one-dimensional projection along a particular direction in the space of the third codon base. The orientations of the three projections are chosen to correspond with the rank ordering of amino acids according to the one-step mutation rings.

**Figure 4:** Siemion’s interpretation of the weight diagram in terms of the rank ordering of ‘one-step mutation rings’. Reproduced from Siemion, 1994a.

**Figure 5:** Least-squares trigonometric fit (dots) to the  $P^\alpha$  conformational parameter (small circles) as a function of mutation angle  $k$ . Crosses (“pref”) denote the fitted function, Eq.(7), evaluated at preferred codon positions.

**Figure 6:** Estimated trigonometric fit (dots) to  $P^\alpha$  (small circles) as a function of  $k$ . Crosses (“pref”) denote the fitted function, Eq.(8), evaluated at preferred codon positions.

**Figure 7:** Polynomial fits (black circles) to the  $P^\alpha$  conformational parameter (white circles) as a function of the six codon coordinates. The fit is given by Eq.(10). Crosses (“modif”): same function, with the  $d_2^2(d_3 - m_3)$  coefficient modified from  $-0.075$  to  $-0.2$  to enhance eight-codon periodicity.

**Figure 8:** Least-squares fit (5 parameters) to the  $P^\beta$  conformational parameter as a function of the six codon coordinates. Small circles: data; dots: least-squares fit given by Eq.(11).

**Figure 9:** Least-squares fit (4 parameters) to relative hydrophilicity (Weber and Lacey, 1978) as a function of the six codon coordinates. Small circles: data; dots: least-squares fit given by Eq.(13).

**Figure 10:** Least-squares fit (2 parameters) to Grantham polarity (Grantham, 1974) as a function of the six codon coordinates. Small circles: data; dots: least-squares fit given by Eq.(12).

Table 1:

	$G_{37}^0$	fit	$R_f$	fit	$R_x$	fit
GG	-3.26	-3.312	0.065	0.0651	0.436	0.436
CG	-2.36	-2.412	0.146	0.166	0.326	0.327
UG	-2.11	-2.085	0.16	0.185	0.291	0.293
AG	-2.08	-1.975	0.048	0.007	0.660	0.656
AC	-2.24	-2.215	0.118	0.162	0.494	0.548
UC	-2.35	-2.245	0.378	0.341	0.218	0.186
CC	-3.26	-3.312	0.349	0.321	0.244	0.22
GC	-3.42	-3.472	0.193	0.216	0.326	0.328
GU	-2.24	-2.175	0.224	0.227	0.291	0.293
CU	-2.08	-2.015	0.359	0.332	0.218	0.186
UU	-0.93	-0.991	0.389	0.352	0.194	0.151
AU	-1.10	-1.161	0.112	0.173	0.441	0.514
AA	-0.93	-0.991	0.023	-0.04	1	0.877
UA	-1.33	-1.391	0.090	0.139	0.441	0.514
CA	-2.11	-2.085	0.083	0.119	0.494	0.548
GA	-2.35	-2.245	0.035	0.014	0.660	0.656

Table 2:

$AA$	$P_\alpha$	$P_\beta$	$P_{Gr}$	$R_f$
ala	1.38	0.79	8.09	0.89
arg	1	0.938	10.5	0.88
asn	0.78	0.66	11.5	0.89
asp	1.06	0.66	13	0.87
cys	0.95	1.07	5.5	0.85
gln	1.12	1	10.5	0.82
glu	1.43	0.509	12.2	0.84
gly	0.629	0.869	9	0.92
his	1.12	0.828	10.4	0.83
ile	0.99	1.57	5.2	0.76
leu	1.3	1.16	4.9	0.73
lys	1.20	0.729	11.3	0.97
met	1.32	1.01	5.7	0.74
phe	1.11	1.22	5.2	0.52
pro	0.55	0.62	8	0.82
ser	0.719	0.938	9.19	0.96
thr	0.78	1.33	8.59	0.92
trp	1.03	1.23	5.4	0.2
tyr	0.729	1.31	6.2	0.49
val	0.969	1.63	5.9	0.85



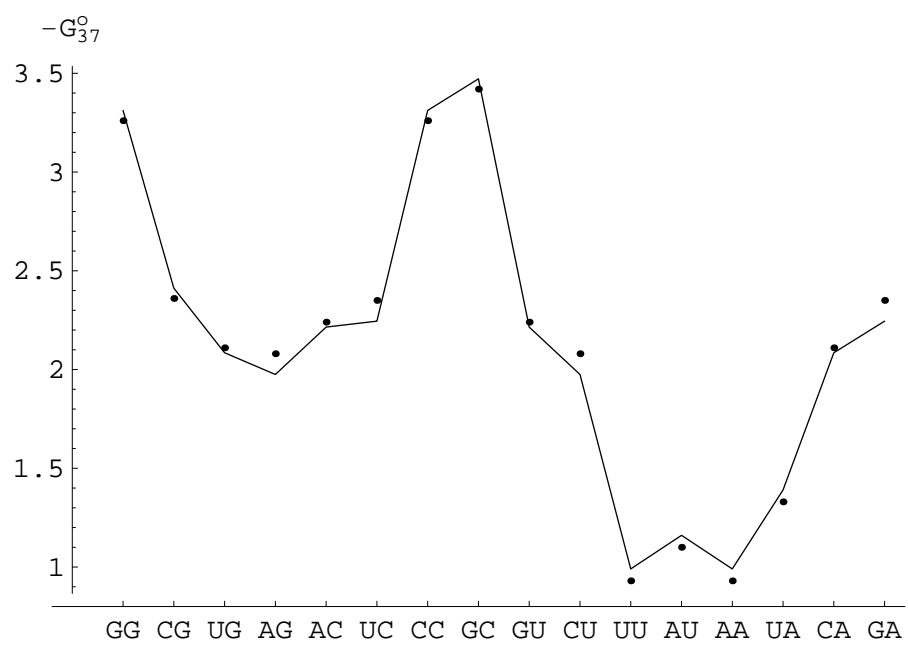


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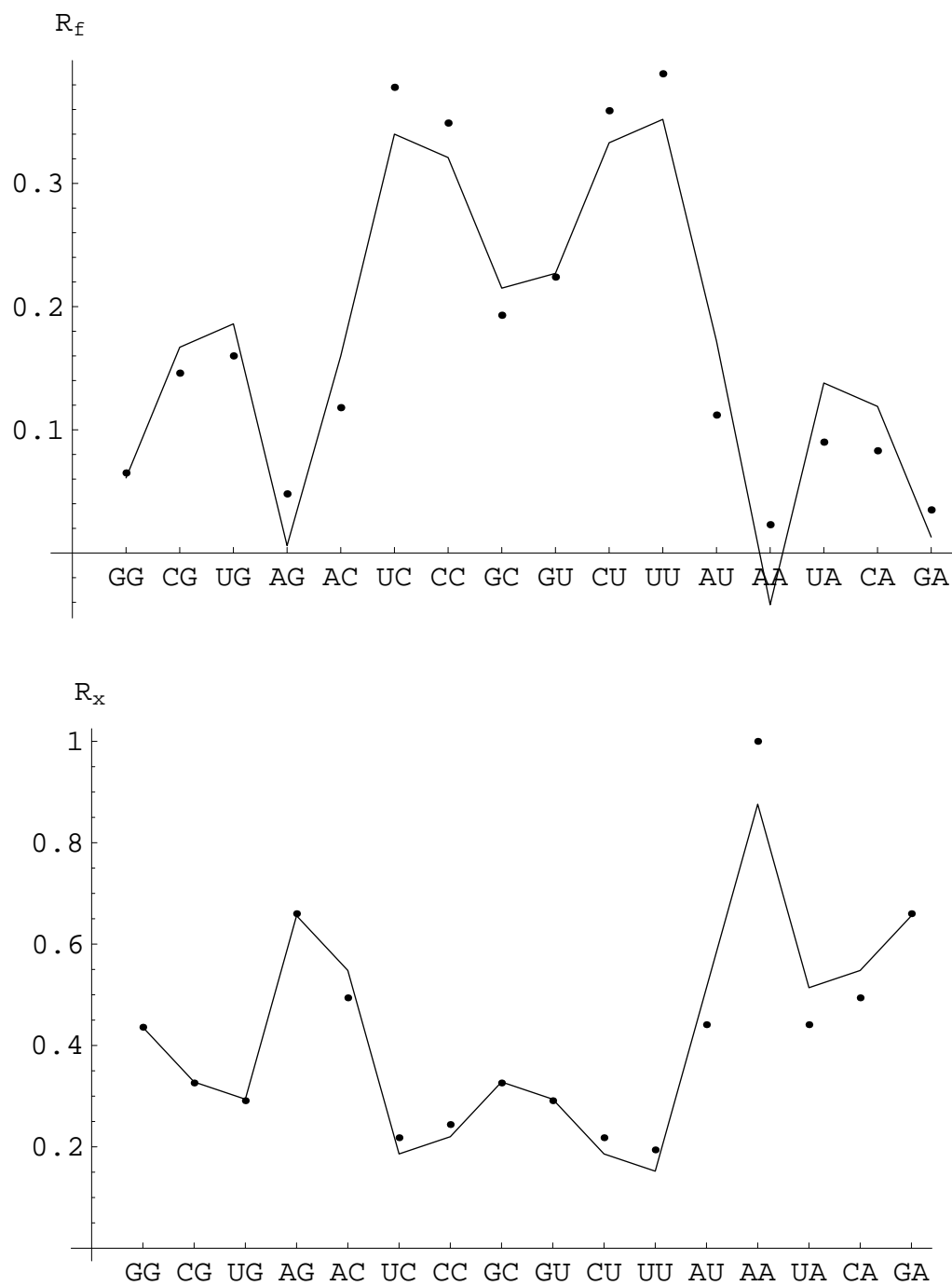


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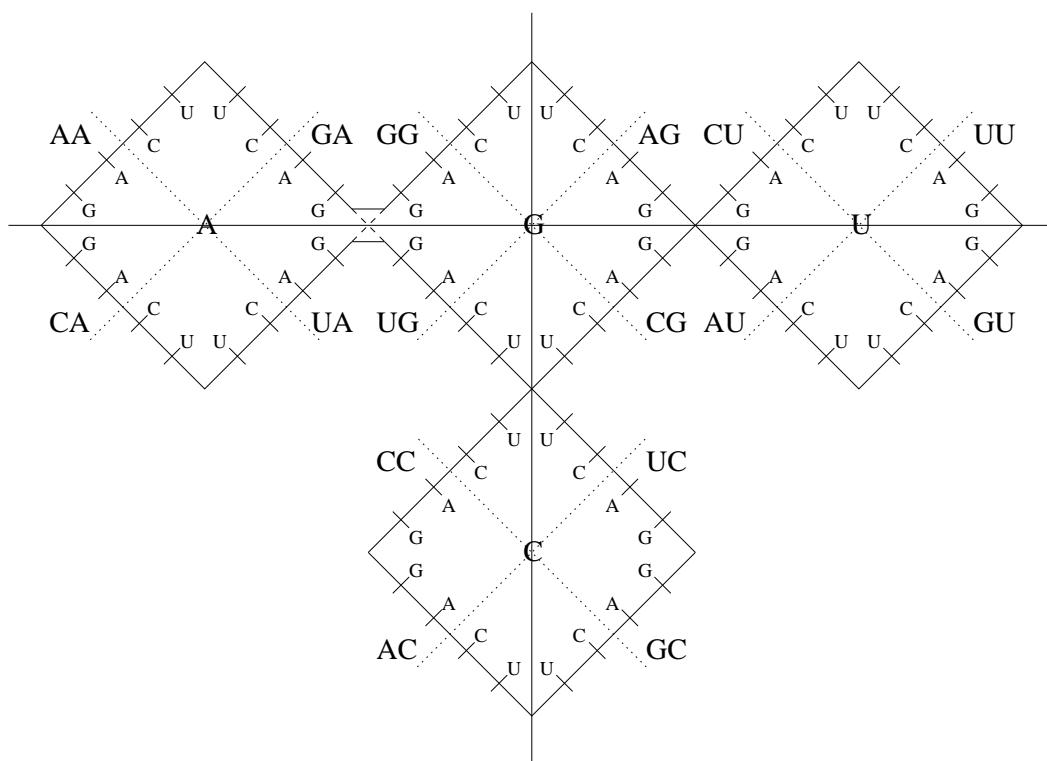


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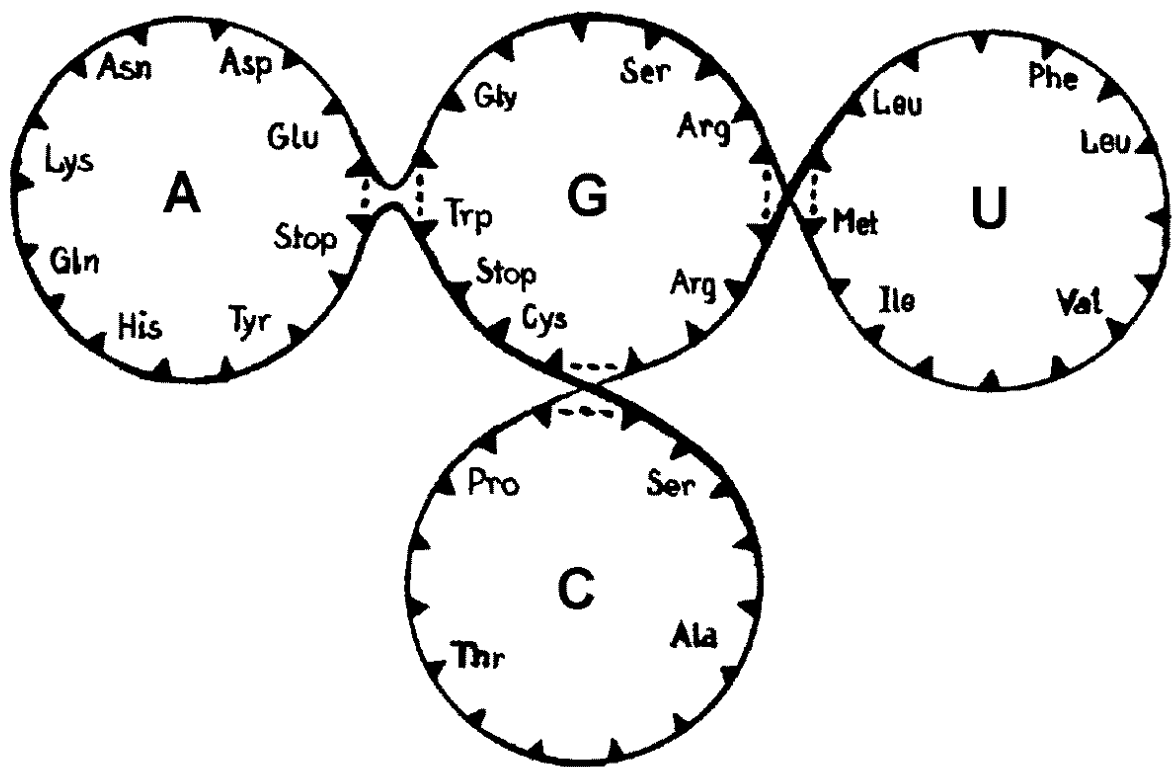


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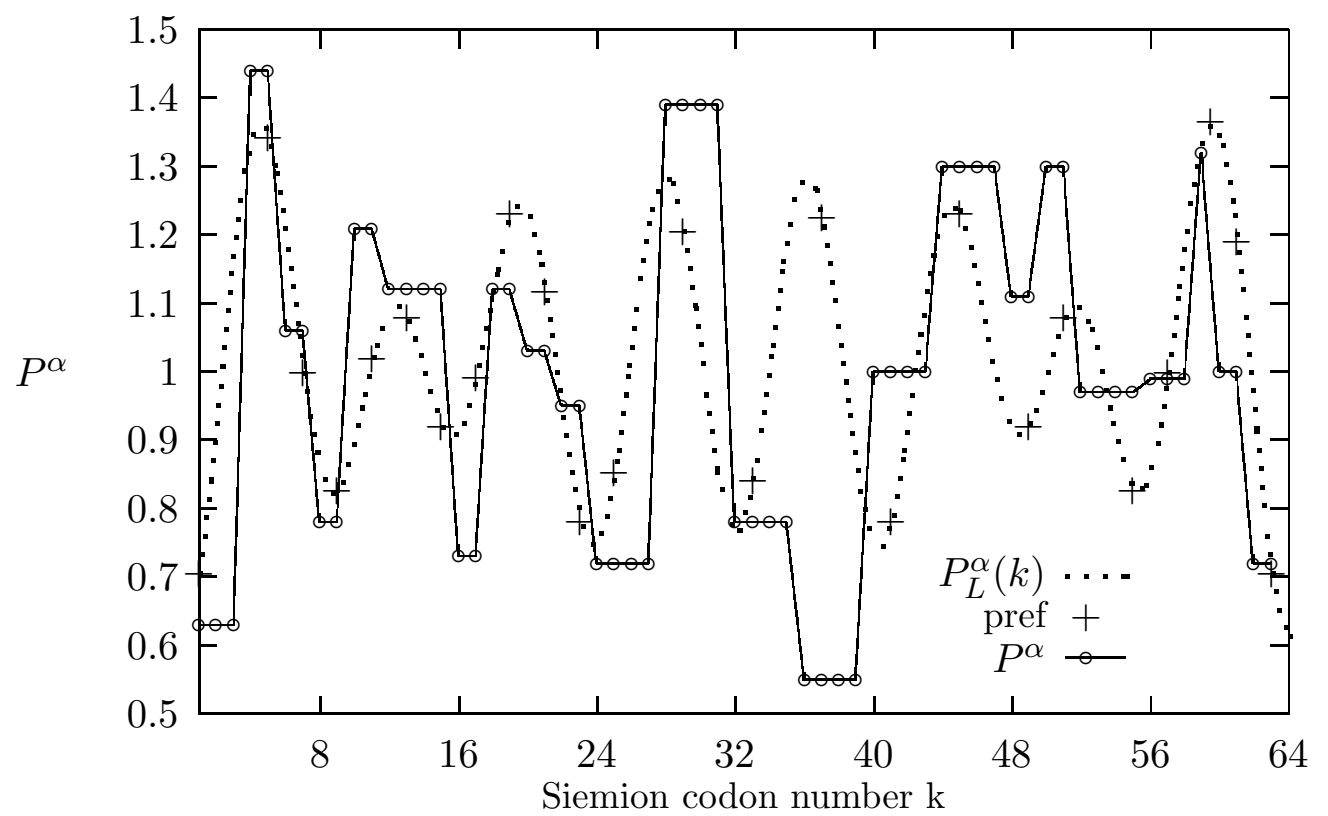


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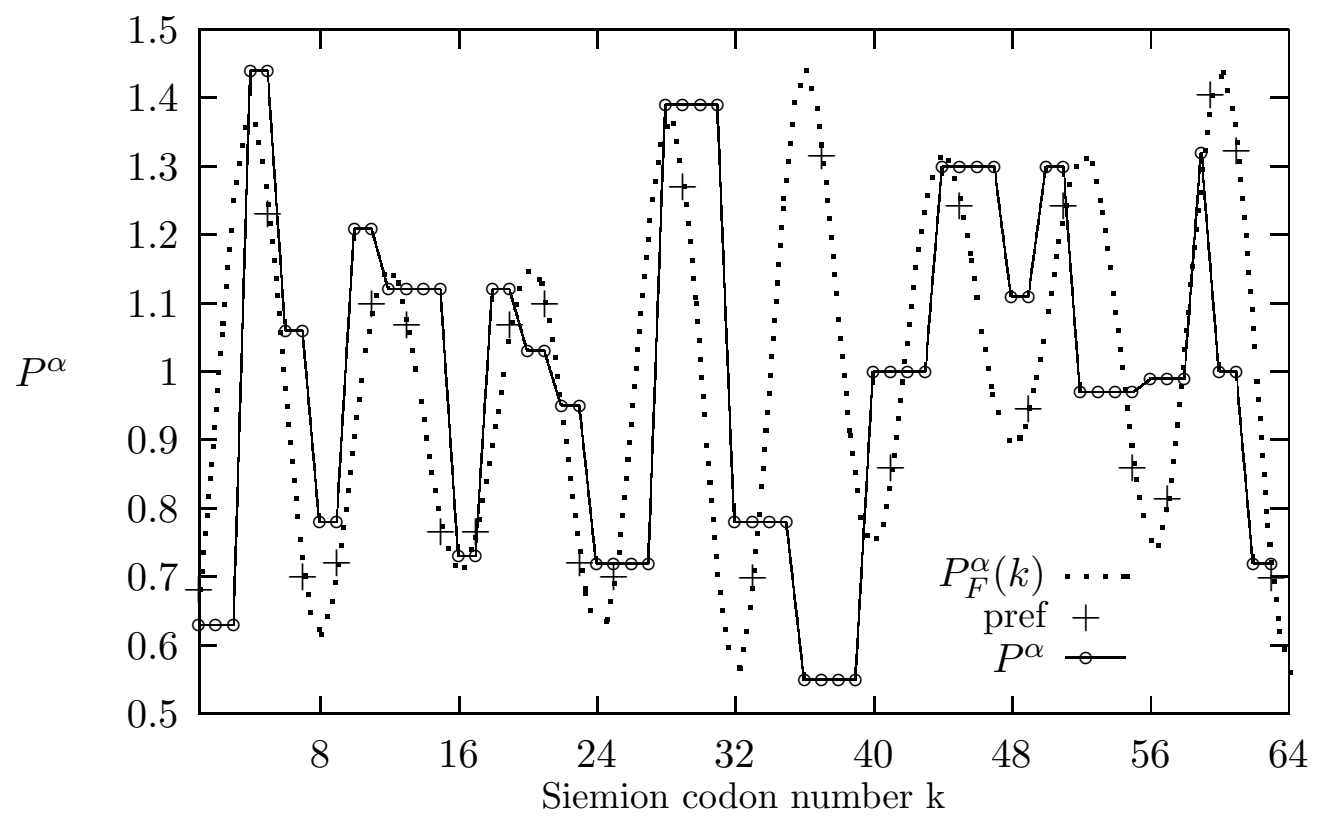


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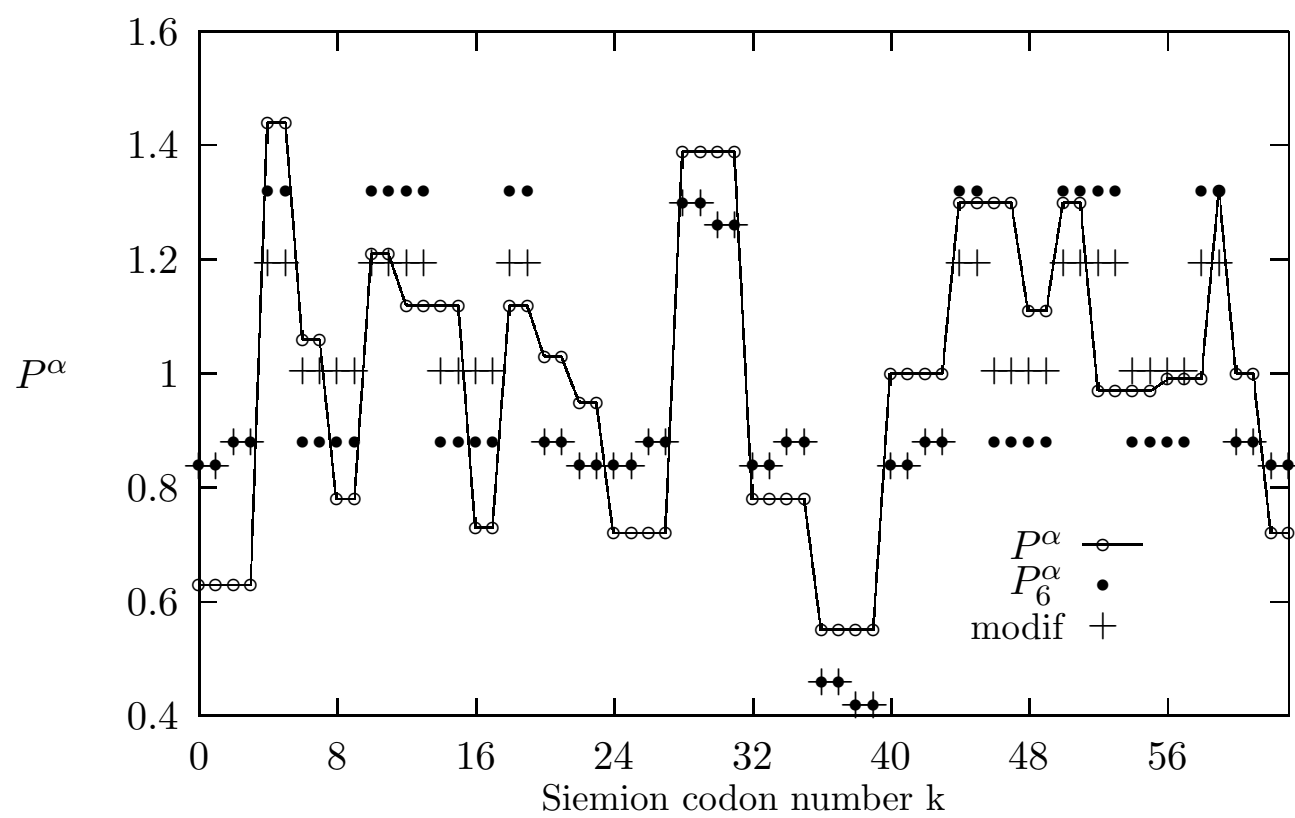


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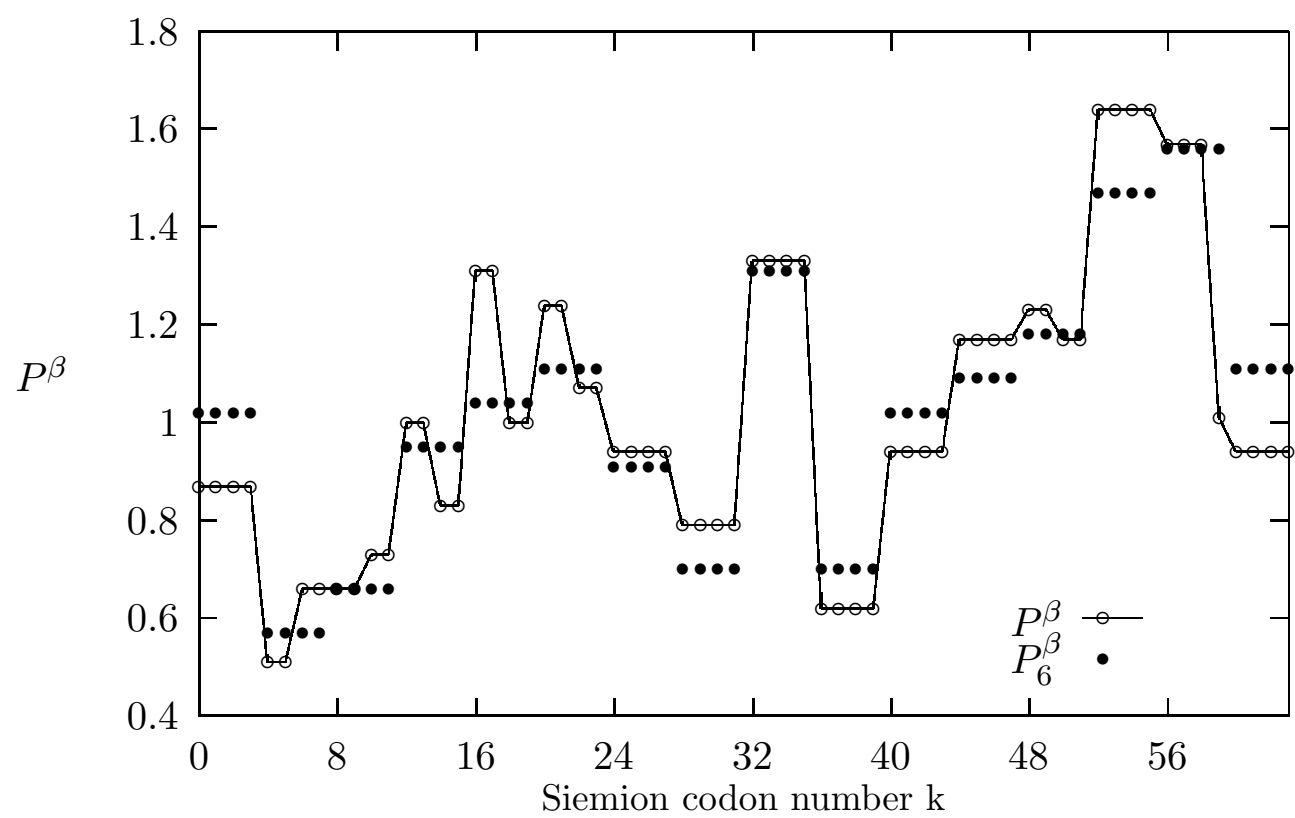


Figure 8:



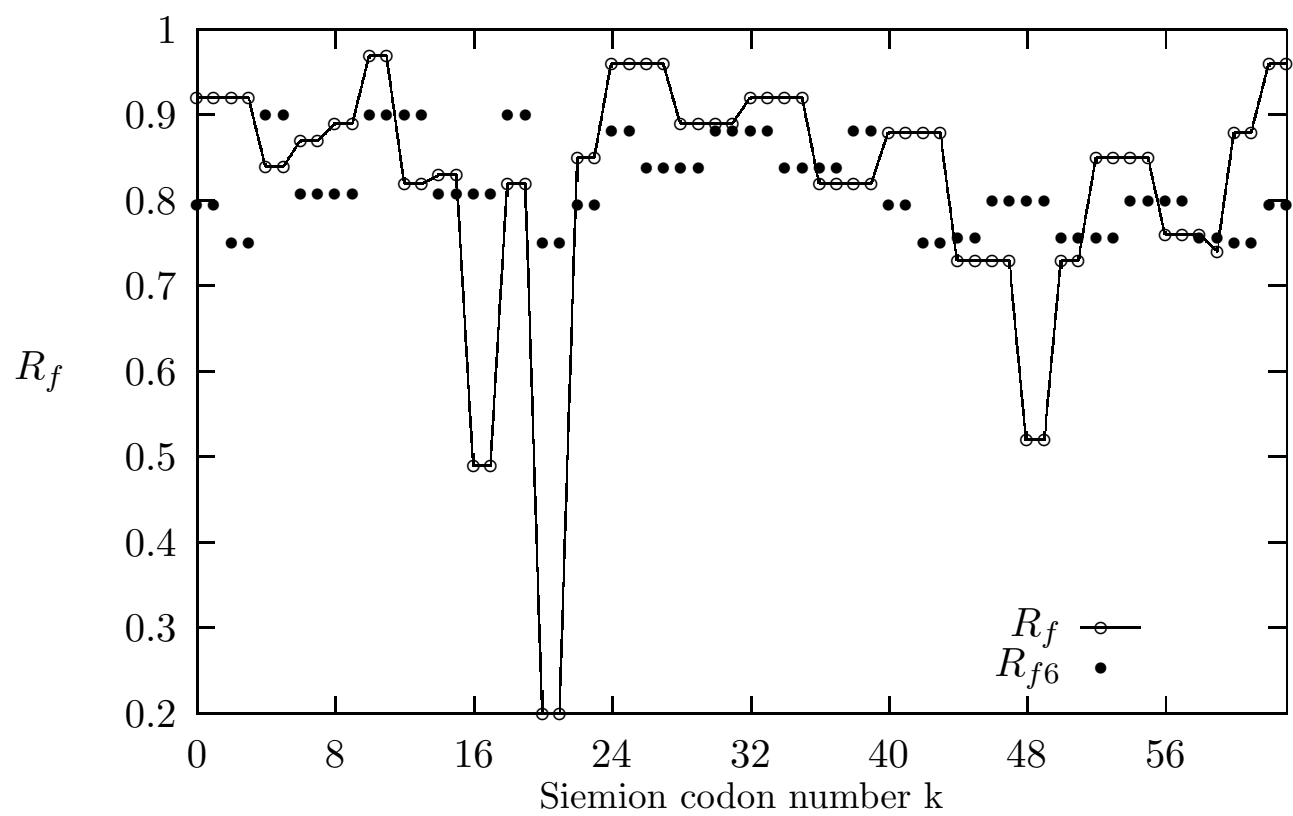


Figure 9:

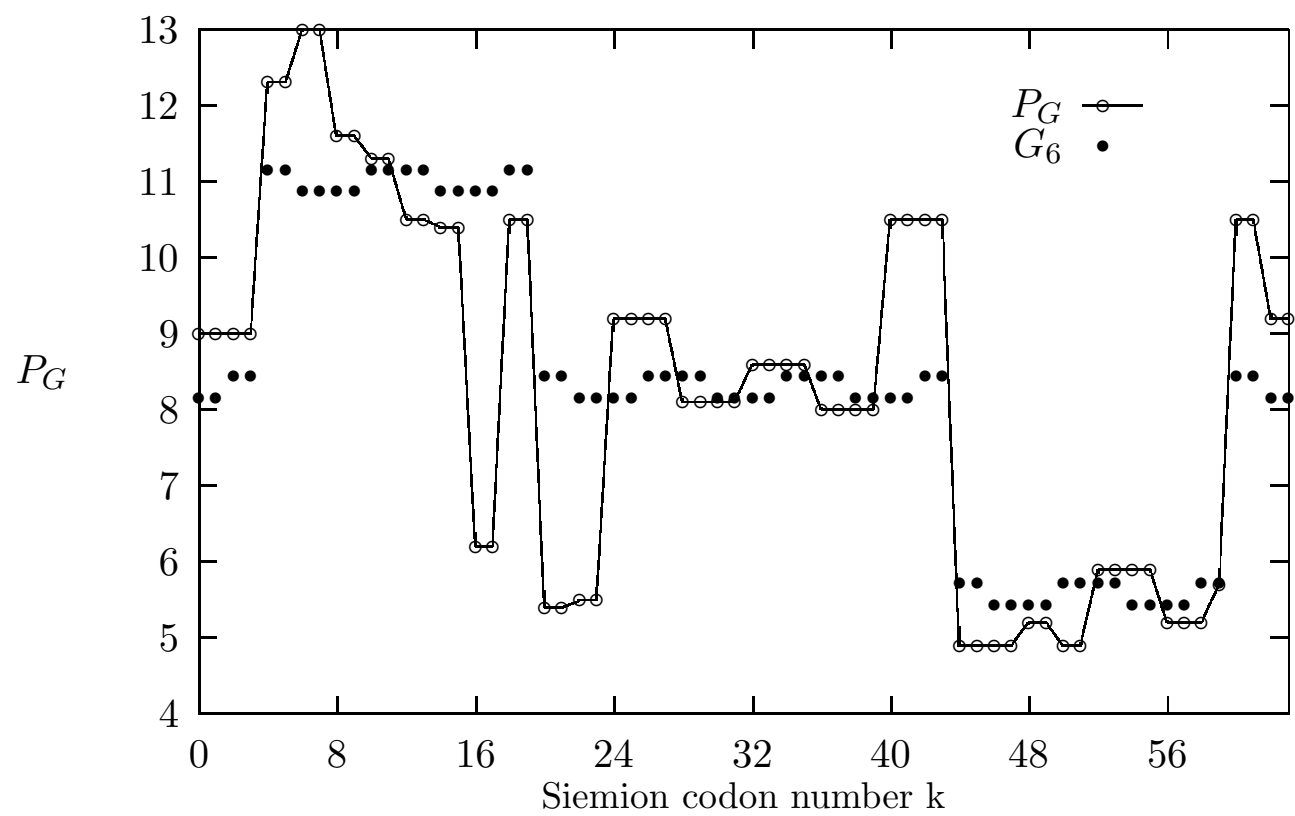


Figure 10: